# EXHIBIT C

## Civamide Nasal Solution

**Two Phase III studies (WL-1001-02-02, WL-1001-02-03)** These studies were double-blind, randomized, placebo-controlled, parallel-group, multicenter studies to evaluate Civamide Nasal Solution 0.01% in the prevention of episodic cluster headaches during an episodic cluster headache period. The studies followed identical protocols to enable pooling of their results. The following discusses the pooled analysis of these studies. Thirty-six (36) sites participated in the United States and Europe, enrolling a total of 112 subjects.

Subjects who had experienced episodic cluster headache for at least two years, with at least two previous episodes and an expected cluster headache period duration of greater that six weeks were enrolled into the Screening Period during a headache free period or at the beginning of a cluster headache period. Subjects were given a diary to be completed at the onset of the next or current cluster headache episode.

The Screening Period was followed by a 3-day Baseline Period during which the subject recorded information in the diary regarding cluster headache onset, duration, severity, symptoms associated with cluster headache and acute medication use for the headache relief. The subject also recorded all concurrent medications taken. Subjects were allowed to remain on prophylactic medications for cluster headache provided the dose regimen was stable for at least 14 days prior to the Baseline Period and the subject agreed to continue on the stable dose throughout the study. The subjects returned to the clinic after the 3-day Baseline Period. The diary was reviewed for completion and clarity. Subjects must have experienced at least one cluster headache (and no more than 8) per day on each of the three days immediately preceding Visit 2 to be eligible for randomization. During this visit, Selection Criteria were reviewed and a headache history and medical history were taken. A general Physical Exam, Physical Inspection of the Nose and Oropharynx and Odor Detection Test were performed and Vital Signs measured.

Subjects meeting all Selection Criteria were randomized 2:1 to Civamide Nasal Solution 0.01% or placebo nasal solution administered twice daily and entered the 7 day Treatment Period. The placebo solution was identical to the Civamide Nasal Solution with the exception of the civamide 100ug/ml being replaced with sodium chloride 10% in the vehicle solution. Subjects were administered the first dose of study drug in one nostril and asked to demonstrate the ability to properly administer the intranasal solution into their other nostril while in the clinic. Subjects were given a diary to record study drug dosing, cluster headache onset, duration, severity, symptoms associated with the cluster headache, acute medication use for the headache relief, concurrent medication usage and adverse experiences. On Day 8, subjects returned to the clinical site, study drug was collected and the diary reviewed for completeness and clarity. A Physical Inspection of the Nose and Oropharynx and Odor Detection Test were performed and Vital Signs measured.

The subjects then entered the 42-day Post-Treatment Observation Period. Subjects were given diaries to complete to record cluster headache onset, duration, severity, symptoms associated with the cluster headache, acute medication use for the headache relief, concurrent medication usage and adverse experiences. The subjects returned a diary by mail on Day 21, and had a clinic visit on Day 35 (Visit 4) during which the diary was reviewed and Vital Signs were measured. At the end of the Post-Treatment Observation Period, Day 49 (Visit 5), a Physical Inspection of the Nose and Oropharynx and Odor Detection Test were performed, and Vital Signs measured. The subject was then discharged from the study.

In the pooled study, 360 subjects enrolled into the Screening Period, of these, 112 subjects randomized to study drug and are included in the Safety Population. There were 101 subjects in the Intent-to-Treat Efficacy Population. The Intent-to-Treat Population consisted of all randomized subjects who had at least one dose of double-blind treatment and who had at least one day of efficacy data during the Post-Treatment Observation Period. The Per Protocol Population consisted of 85 subjects. The Per Protocol Population consisted of all

randomized subjects who had a diagnosis of episodic cluster headache, had at least one cluster headache per day during the three-day baseline period, had an anticipated duration for the current episode of at least four weeks beyond Day 1, had received at least three days of double-blind treatment, and had at least seven days of diary data in the Post-Treatment Observation Period.

The primary efficacy variable was the Percent Change in the Number of Cluster Headaches from Baseline to Weeks 1 through 4 summarized separately for the Intent-to-Treat and the Per Protocol Populations. Secondary efficacy variables were preformed on the Intent-to-Treat and Per Protocol Populations and include: the Percent Change in the Number of Cluster Headaches per Week from Baseline to Weeks 1 through 3, and Individual Weeks 1 to 6; the Number of Cluster Headaches per Week and the Change in the Number of Cluster Headaches per Week from Baseline to Weeks 1 through 4 and Individual Weeks 1 to 6; the Requirement for Acute Medication Usage; the Average Cluster Headache Severity during the Post-Treatment Period; the Average Duration of Cluster Headaches; and the Presence of Cluster Headache Symptoms.

The incidence of adverse events was the primary safety endpoint.

A single week of treatment, the use of Civamide Nasal Solution 0.01% resulted in a clinically significant decrease in the frequency of cluster headache. For the ITT Population, there was a greater decrease in the civamide treatment group, 45.0% in the primary efficacy parameter, the Percent Change in the Number of Cluster Headaches per Week from Weeks 1 through 4 Compared to Baseline than in the placebo treatment group 29.8%, the difference between treatment groups did not reach statistical significance, p=0.2738. For the PP Population, there was even a greater decrease in the civamide treatment group compared to the placebo treatment group, 53.7% vs. 26.7%, which did approach significance with p= 0.0670. In the group treated with Civamide, the frequency of cluster headaches declined continuously over the 42-day Post-Treatment Period with civamide treated patients having a 65% reduction in headaches by week 6.

There were no serious adverse events reported that were attributed to the study drug. There were only 3 systemic adverse events that were classified as "probably related" occurred during the Treatment Period and were Nausea in one subject in each treatment group and Sweating Increased in one subject in the civamide treatment group. There were more adverse events reported in the civamide treatment group (90%) than in the placebo treatment group (71%), a difference that was statistically significant, p= 0.0167. The difference was accounted for by more subjects in the civamide treatment group reporting Application Site Burning (72% vs. 32%, $p < 0.001$) and Lacrimation Increased (51% vs. 7%, $p < 0.001$). There were no other adverse events reported that approached statistical significance between treatment groups. Most adverse events reported were of mild to moderate intensity and of limited duration. Four civamide treatment group subjects (6%) and none of the placebo treatment group subjects discontinued treatment due to intolerability of study drug subjects. Civamide Nasal Solution 0.01% was found to be a generally well tolerated and safe treatment for episodic cluster headache.

**Phase II/III study (WL-1001-02-01)** This was a double-blind, vehicle controlled study, conducted to evaluate the safety and efficacy of Civamide Nasal Solution for the prophylaxis and treatment of episodic cluster headaches. There were 8 sites that enrolled 28 subjects.

The study consisted of a seven-day Treatment Period and a 20-day Post Treatment Period. At the subject's initial visit (Day 1), eligibility for the study was ascertained. Subjects at least 18 years of age with at least a two-year history of cluster headaches with one to three cluster periods over the two previous years and at least one headache daily on each of the three days prior to entry were eligible for the trial. Headaches had to meet slightly modified International Headache Society Diagnostic Criteria for episodic cluster headache (i.e., 15 to 240 minute headache duration untreated). Eligible subjects were assigned to treatment groups, using a 2:1 randomization. Study medication consisted of Civamide Nasal Solution 0.025% (250 µg /ml) and vehicle. 0.1 ml delivered intranasally to each nostril.

Subjects received diaries for subjective self-evaluation of pain intensity, associated symptoms and adverse experiences, along with explanations concerning completion of these assessments, for each of the 27 days of the study. Subjects were also asked to fill out diaries regarding their overall satisfaction with the study medications, particularly as compared to medications they have previously used, using a seven point categorical scale. The efficacy endpoints of primary interest were based on the total number of headaches during the Post Treatment Period and include the percent change and change in the number of headaches from Baseline. Secondary efficacy endpoints included: the number of headaches experienced during each week of the Post Treatment Period, pain intensity, presence or absence of associated symptoms and subject's assessment of effectiveness of study medication.

The incidence of adverse experiences was the primary safety endpoint of the study. Secondary safety endpoints included the incidence of "treatment-related" adverse experiences classified according to preferred term and body system; an odor detection test; an examination of nasal mucosa; laboratory tests and EKG abnormalities.

Civamide Nasal Solution was effective in reducing the number of headaches as evidenced by the percent reduction in the mean number of weekly headaches in the Post Treatment Period (Days 1-20). The mean number of weekly headaches for the ITT Civamide group in this period is 4.6, representing a mean decrease of 7.8 from a Baseline mean of 12.4, and a mean percent reduction of 63.4%. The mean number of weekly headaches for the ITT Vehicle group in this period is 7.2, representing a mean decrease of 3.5 from a Baseline mean of 10.8, and a mean percent reduction of 30.3%. The p-value for the difference between the two treatment groups in the percent change is 0.0198. Reductions in severity or numbers of associated headache symptoms were also in favor of civamide, but not statistically significant.

There were no clinically significant changes in vital signs, ECG or laboratory results. All subjects could detect the test odor at both visits and there were no significant differences between the treatment groups with respect to the examination of the nasal mucosa. The most common adverse experiences included nasal burning, experienced by 78% (14/18) of the Civamide group vs. 10% (1/10) of the Vehicle group ($p=0.001$). Lacrimation was experienced by 50% (9/18) of the Civamide group vs. 0% of the Vehicle group ($p=0.10$). Rhinitis or pharyngitis was experienced by 50% (9/18) of the Civamide group vs. 20% (2/10) of the Vehicle group, however this difference was not significant ($p=0.226$). No serious adverse events were reported for any subjects.